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Tyvaso DPI: Drug-device characteristics and patient clinical considerations

Colleen McEvoy [a], Rahul Argula [b], Sandeep Sahay [c], Shelley Shapiro [d], Christina Eagan [e], Anthony J. Hickey [f], Chad Smutney [g], Chris Dillon [h], Thomas Winkler [h], Brittany N. Davis [h], Meredith Broderick [h], Charles Burger [i,*]

[a] Division of Pulmonary and Critical Care Medicine, Washington University in St. Louis, St. Louis, MO, USA
[b] Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Medical University of South Carolina, Charleston, SC, USA
[c] Division of Pulmonary, Critical Care & Sleep Medicine, Houston Methodist Hospital, Houston, TX, USA
[d] Cardiology Division, Greater Los Angeles VA Healthcare System, Department of Pulmonary Critical Care, David Geffen UCLA School of Medicine, Los Angeles, CA, USA
[e] Division of Pulmonary, Critical Care, and Sleep Medicine, University of Florida, Gainesville, FL, USA
[f] RTI International, Research Triangle Park, NC, USA
[g] MannKind Corporation, Danbury, CT, USA
[h] United Therapeutics Corporation, Research Triangle Park, NC, USA
[i] Division of Pulmonary, Allergy and Sleep Medicine, Mayo Clinic, Jacksonville, FL, USA

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ABSTRACT

Tyvaso DPI is a drug-device combination therapy comprised of a small, portable, reusable, breath-powered, dry powder inhaler (DPI) for the delivery of treprostinil. It is approved for the treatment of pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease. Tyvaso DPI utilizes single-use prefilled cartridges to ensure proper dosing. Unlike nebulizer devices, administration of Tyvaso DPI is passive and does not require coordination with the device. The low-flow rate design results in targeted delivery to the peripheral lungs due to minimal drug loss from impaction in the oropharynx. The inert fumaryl diketopiperazine (FDKP) excipient forms microparticles that carry treprostinil into the airways, with a high fraction of the particles in the respirable range. In a clinical study in patients with pulmonary arterial hypertension, Tyvaso DPI had similar exposure and pharmacokinetics, low incidence of adverse events, and high patient satisfaction compared with nebulized treprostinil solution. Tyvaso DPI may be considered as a first prostacyclin agent or for those that do not tolerate other prostacyclin formulations, patients with pulmonary comorbidities, patients with mixed Group 1 and Group 3 pulmonary hypertension, or those that prefer an active lifestyle and need a portable, non-invasive treatment. Tyvaso DPI is a patient-preferred, maintenance-free, safe delivery option that may improve patient compliance and adherence.

1. Introduction

Pulmonary arterial hypertension (PAH) and pulmonary hypertension associated with interstitial lung disease (PH-ILD) are both forms of precapillary PH [1–6]. Right heart catheterization is required to confirm an elevated mean pulmonary pressure >20 mmHg, pulmonary vascular resistance >2 Wood units, and pulmonary arterial wedge pressure ≤15 mmHg [2,4,7,8]. Although both PAH and PH-ILD share similar hemodynamic criteria, the distinction between the two is the presence of underlying lung disease [5,6]. As both PAH and PH-ILD are life-threatening, progressive diseases that can lead to right ventricular failure and death, an effective, convenient treatment is important to minimize disease impact and improve patients' quality of life. Synthetic prostacyclin analogs are a mainstay of PAH therapy as they have been shown to improve hemodynamics, exercise tolerance and overall survival in patients with PAH [9].

Nebulized Tyvaso (treprostinil solution for inhalation) is a prostacyclin mimetic approved for the treatment of PAH and PH-ILD to improve exercise ability [10,11]. Prior to the approval of Tyvaso, there were no approved therapies for PH-ILD as all previous randomized controlled trials failed to meet the pre-specified primary endpoints [12–19]. However, nebulized Tyvaso can be time consuming and cumbersome due to the need for device preparation, maintenance, and duration of treatment, which prompted the development of the

* Corresponding author.
E-mail address: burger.charles@mayo.edu (C. Burger).

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handheld, portable drug-device combination to enhance the usability of inhaled treprostinil.

Tyvaso DPI is a drug-device combination therapy comprised of a dry powder formulation of treprostinil, previously referred to as treprostinil Technosphere (TreT), and a small, portable, reusable, maintenance-free, breath-powered, dry powder inhaler (DPI) device (Dreamboat®) [10]. This new product provides a simple, convenient option for patients and produces comparable levels of systemic exposure of treprostinil to the Tyvaso nebulizer inhaled formulation [20,21].

Inhaled treprostinil therapy provides direct targeted delivery to the lung vasculature, resulting in immediate local drug availability with minimal systemic exposure, potentially minimizing systemic adverse events (AEs) associated with parenteral and oral prostacyclin therapy [22–24]. Inhaled treprostinil results in clinical improvements in patients with PAH and PH-ILD, as well as hemodynamic improvement in patients with PAH [21,25–27]. Further, delivery of treprostinil to the alveolar space in the healthy non-fibrotic parts of the lung reduces the risk of ventilation-perfusion mismatching within the lung, particularly in patients with underlying lung disease [28].

Tyvaso DPI aims to be simpler for patient use than the conventional nebulizing delivery method by improving ease-of-use, storage, and portability with a maintenance-free, handheld, low flow device. The device aspects of Tyvaso DPI may also enhance patient compliance and quality of life [21]. The characteristics of and clinical experience with Tyvaso DPI, and relevant patient characteristics that should be considered for appropriate use with this device are further explained in this review.

2. Components and technical characteristics of Tyvaso DPI

2.1. Drug particle technical characteristics

Tyvaso DPI powder has two formulation components: treprostinil and a single, inert excipient, fumaryl diketopiperazine (FDKP). Treprostinil is a stable tricyclic analog of the naturally occurring prostacyclin (PGI_2) and exerts its pharmacological actions via prostanoid receptors IP, DP_1, and EP_2 [29,30]. Tyvaso DPI has a quick onset of action (C_{max}: 0.39–1.33 ng/mL; T_{max}: 10 min) [10,23,31].

FDKP facilitates deposition in the peripheral lungs, increasing overall exposure to treprostinil. FDKP was first developed by MannKind Corporation for use with the Afrezza inhalation powder, an insulin dry powder [32]. The attributes of the FDKP excipient make it well-suited

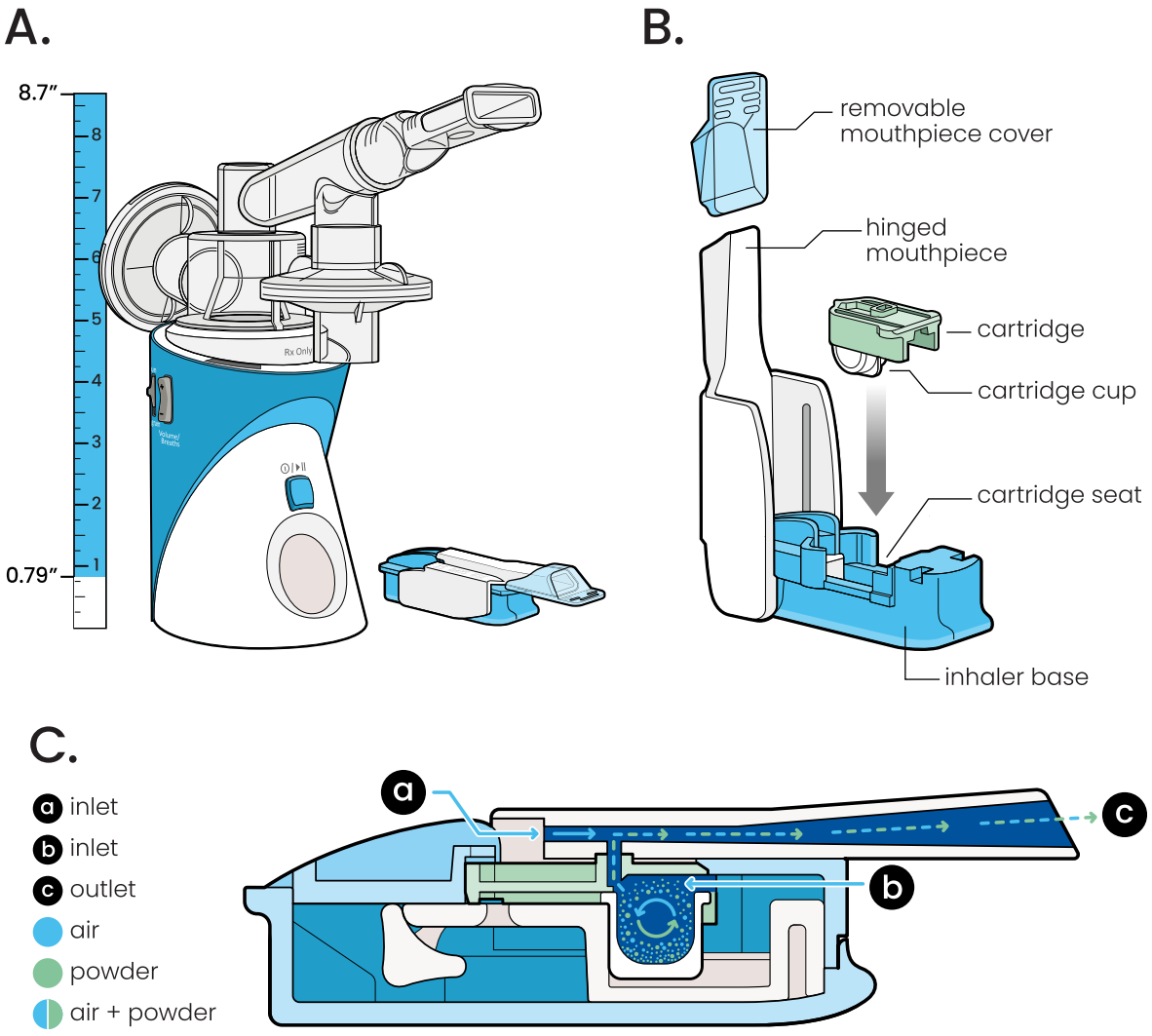

Fig. 1. Airflow through Tyvaso DPI.
A) Size comparison of the Tyvaso Inhalation System for delivery of nebulized treprostinil compared with the Tyvaso DPI. B) Components of Tyvaso DPI inhaler. C) Dual airflow through Tyvaso DPI. The pressure within the device is created by the patient's inhalation and no other action or coordination is required. Air flow through the inlet (b) deagglomerates the bulk powder in the cartridge until it is small enough to pass through the exit port. The airflow through the top inlet (a) provides a final shearing force to ensure the drug particles are the proper size and air flow is suitable to drive the drug powder into the lungs (c).

for lung delivery. For example, FDKP does not accumulate in the lungs; rather it rapidly dissolves in the neutral pH of the lung [31,32], whereas other excipients can accumulate in the lungs with repeated dosing, negatively impacting lung function [33]. Additionally, FDKP is not a penetration enhancer, such as detergents which increase drug permeability by dilating tight junctions, opening paracellular pathways, and disrupting plasma membranes. These detergents may result in subsequent inflammation through a potentially cytotoxic mechanism [31, 34–36]. Rather, FDKP particles are readily and easily absorbed through the lung, unchanged after clearance, and undergo renal excretion [37]. FDKP has not been associated with a decline in forced vital capacity, bronchospasm, or other pulmonary events [38].

2.2. Device technical characteristics

Tyvaso DPI utilizes single-use, prefilled cartridges, allowing for dosing to be achieved with one breath per cartridge. Notably, the inhaler has a maintenance-free, one-week in-use period after which it is discarded and replaced [39]. The inhaler has a resistance value of 0.090 $kPa^{1/2}$/L/min and consists of a mouthpiece, a removable mouthpiece cover, cartridge, and base (Fig. 1b; see Table 1 for the device size). Dispersing airflow through the device occurs when a user inhales through the DPI mouthpiece. This creates two airstreams that are designed for a complete dispersal of the drug from the cartridge into the lungs in one breath (Fig. 1c). One airstream moves through the cartridge to fluidize, tumble, and disperse the powder from the cartridge into the second airstream. The second airstream intersects the first, providing a focused, shearing action to make the powder respirable before leaving the device. The airstreams and their subsequent flow mechanics are tuned to facilitate a rapid emptying and dispersion of the powder microparticles after the onset of the patient's inhalation. Powder dispersion typically occurs in less than 0.5 s with less than 500 mL of inhaled air volume. Low inhalation pressures generated by the user in the order of 2–4 kPa are efficient to induce low-flow rates around 20 L/min (16–22 L/min) through the DPI. The device permits the delivery of 16, 32, 48, or 64 μg doses of treprostinil in one breath (Table 2) [20]. For doses beyond 64 μg, two cartridges are taken to reach the prescribed dose; however, higher-strength cartridges are currently under development. Tyvaso DPI provides a more compact option for patients than the previous Tyvaso nebulizer and produces comparable pharmacokinetics (Table 1) [20].

Table 2
Comparison of Tyvaso DPI and Approximate Tyvaso nebulizer dosages [10].

Tyvaso DPI Cartridge Strength[a]	Tyvaso Nebulizer Number of Breaths
16 μg	≤5 (≤30 μg)
32 μg	6 to 7 (36–42 μg)
48 μg	8 to 10 (48–60 μg)
64 μg	11 to 13 (66–72 μg)
80 μg	14 to 16 (78–90 μg)
96 μg	17 to 19 (96–112 μg)
112 μg	20 to 22 (118–130 μg)
128 μg	23 to 25 (136–148 μg)
144 μg	26 to 28 (154–166 μg)
160 μg	29 to 31 (172–184 μg)
176 μg	32 to 34 (190–202 μg)

[a] Doses of ≥80 μg requires the use of ≥2 cartridges.

3. Pulmonary drug delivery of Tyvaso DPI

The magnitude of drug deposition in the lungs with DPI devices varies due to multiple properties of the powder formulation and device. For drugs to reach the peripheral lungs, the powder must be within an optimal aerodynamic range for deposition into the target area [22,40]. Previously it has been shown that the optimal size for pulmonary deposition is 1–5 μm [41–44]. Finally, the patient must be capable of creating the inhalation pressure drop required to use the device. As the flow mechanics within the DPI have been designed to complement the FDKP microparticles, powder delivery is efficient. The particle size distribution of Tyvaso DPI is well-suited for deposition in the bronchioles in the distal lung.

3.1. Particle parameters

The particle size distribution profile of Treprostinil-FDKP microparticles for the 16th, 50th, and 84th percentiles are 1.7, 2.6, and 4.0 μm, respectively [45,46]. FDKP microparticles have a large surface area

Table 1
Comparison between Tyvaso DPI and treprostinil nebulizer.

	Tyvaso DPI [10]	Treprostinil Nebulizer [11]
Battery	No battery needed.	Battery charged when not in use and in between uses. The battery may take up to 8 h to fully charge.
Setup	Insert single-use cartridge and inhale. Reusable inhaler is replaced every 7 days, no cleaning required.	Place one ampule of Tyvaso in nebulizer device's medicine cup. Each ampule contains enough medicine for all four sessions each day. Set up device 1× each morning. Clean device 1× each night.
Dosing	Inhale 1 breath per cartridge 4× daily. Each dose is inhaled in 2 s. Cartridge strengths vary and can be found on the next row.	1 breath is equal to 6 μg. 4× daily. Each treatment session takes approximately 2–3 min.
Dosage forms	16 μg cartridge. 32 μg cartridge. 48 μg cartridge. 64 μg cartridge. Cartridge strengths can be combined to achieve higher doses.	2.9 mL ampule (0.6 mg/mL).
Titration	Increase dose by 16 μg per treatment session at approximately 1- to 2-week intervals. Minimum titration increment corresponds to ~3 nebulizer breaths.	Increase dose by an additional 3 breaths per treatment session, 4 times daily at approximately 1- to 2-week intervals. Increase the number of breaths per session every week to a target maintenance dose of 9–12 breaths. Minimum titration increment is 1 breath.
Device dimensions	3.04″ L × 0.83″ W × 0.79″ H.	3.5″ L × 3.2″ W × 4.7'' H (without attachments added).
Inhalation technique	Each breath should last at least 2 s, holding breath for as long as it is comfortable for the user. Exhale and continue to breath normally.	Each breath should last approximately 3 s, breathing normal full breaths. Do not hold breath and exhale normally.
Storage considerations	Once the pack is opened, cartridges may be stored at room temperature for 8 weeks or under refrigeration until expiration; unopened cartridges must be used within 3 days.	Must be stored in unopened foil pouch at 20–25 °C. Once the foil pack is opened, ampules should be used within 7 days; unopened ampules should be stored in the foil pouch.

DPI, dry powder inhaler.

and high porosity, allowing for the effective delivery and adsorption of drug substances [31,37].

The small size of the microparticles allows the drug product to be delivered to the peripheral lungs [40,47]. Inhalation powders comprising these microparticles are low-density and highly dispersible. After inhalation, the microparticles are rapidly dissolved in the lung, allowing the drug to be swiftly delivered and absorbed into the pulmonary circulation without the need for excessive physical break-up within the device [40,48]. This design allows for consistent, high rates of drug delivery to the targeted areas [40].

Other commonly used excipients were not chosen for the formulation due to aerodynamic properties. Often with DPI formulations, such as ones that use a lactose excipient, the active drug needs to detach from the excipient for the drug to be delivered into the lower respiratory tract while the larger, heavier excipient deposits in the mouth and throat. Drug losses can occur if the active ingredient does not fully separate from the excipient and is deposited in the oropharynx where it will not contribute to the therapeutic effect [40,49]. In addition to reduced pulmonary delivery, greater oropharynx impaction may also increase cough and throat irritation, further reducing the distribution of particles to the lungs [50].

3.2. Device parameters

DPI devices are actuated by the inspiratory pressure generated by the patient when they inhale. The pressure and the resistance level interact to produce a resultant flow rate that must fluidize, de-agglomerate, and disperse the inhalation powder into the lungs. With DPIs, particles deposit in different regions depending on their aerodynamic size and velocity. Particles moving at a high velocity due to high-flow rates are more likely to impact the upper respiratory tract, while particles moving at a lower velocity due to low-flow rates are better able to be distributed throughout the peripheral lungs.

Most DPI devices require high-flow rates (typically in excess of 50 L/min), which patients with airflow limitations and conditions like PAH and PH-ILD may not be able to produce [51]. Tyvaso DPI has been designed with flow mechanics tailored for de-aggregating and dispersing the treprostinil inhalation powder using low-flow rates. Fig. 2 presents flow rate resistance curves covering a range of pressure drops that are typically achievable by patients (1–4 kPa) [52]. Devices that operate at low-flow rates are less affected by a patient's airway resistance or the inspiratory pressure generated by the patient. Instead, they rely on the intrinsic resistance of the device (i.e., the resistance encountered by airflow within the device), resulting in low particulate speeds and ultimately less variability of drug distribution [53,54].

The low-flow attribute of Tyvaso DPI is important because low-flow delivery promotes the deposition of fine particles in the peripheral lungs rather than impacting the oropharynx, thereby increasing the amount of drug distributed to the smaller airways (see Fig. 3) [22,55–57]. With a low-flow device, such as Tyvaso DPI, the dispersed inhalation powder moves slowly with less inertia thereby reducing inertial losses and increasing the amount of the drug to be delivered to the peripheral lungs. In contrast, powders delivered with a low resistance move faster with greater inertia, thereby resulting in greater variability in drug delivery [53]. Flow rates and particle deposition can be likened to a car driving around a curve. Similar to how a fast-moving car struggles to make a turn when speeding, particles moving at high speeds may encounter difficulties navigating the curves of the upper airways, leading to impact there. On the other hand, slower-moving particles can more easily reach the peripheral lungs, just as a slower car can maneuver the same turn more smoothly. The low-flow delivery with Tyvaso DPI enables the added benefit of sustained flow rate post dispersion from the inhaler since the lungs fill more slowly during the administration. This promotes a driving effect of the powder into the lungs that is prolonged when compared to using a high-flow device.

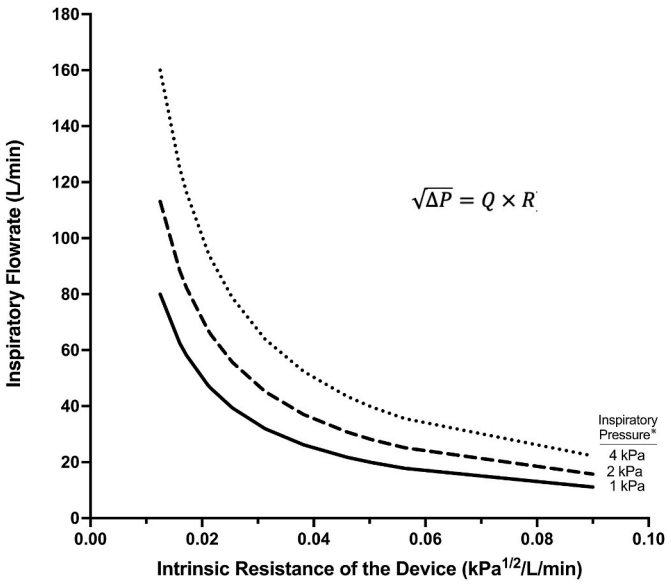

Fig. 2. Relationship between the intrinsic resistance of dry powder inhalers and inspiratory flowrate. Tyvaso DPI is a low-flow, high-resistance device (0.09 kPa$^{1/2}$/L/min) that needs a peak inspiratory pressure of 2 kPa for > 2 s in a single breath to properly disperse the drug. Change in inspiratory pressue is denoted as ΔP; inspiratory flowrate is denoted as Q; intrinsic resistance of the device is denoted as R. Figure adapted from Clark AR et al. The confusing world of dry powder inhalers: It is all about inspiratory pressure, not inspiratory flow rates. *J Aersol Med Pulm Drug Deliv*. 2020; 33(1):1-11. Licensed under CC BY-NC 4.0.

3.3. Breathing parameters

Flow rate is limited by a patient's ability to generate the pressure drop (measured as peak inspiratory pressure; PIP; ΔP) during inhalation ($\sqrt{\Delta P} = Q \times R$), where Q denotes the flowrate and R denotes the intrinsic resistance of the inhaler [55]. A higher PIP increases the likelihood of patients achieving an acceptable inhalation profile [54]. The minimum PIP needed to create adequate powder dispersion to empty the Tyvaso DPI cartridge is 2 kPa for ≥2 s, resulting in complete dose delivery from the device [58–60].

Patients with PAH may have significant respiratory muscle dysfunction and weakness, limiting their maximum inspiratory pressure [61,62]. However, studies of patients with PAH have found the average maximum inspiratory pressure for men and women with PAH is 6.2 ± 2.6 kPa and 5.3 ± 2.0 kPa, respectively, well within the range needed for Tyvaso DPI device [51]. Further, a study in 18 patients with PAH demonstrated those patients were able to achieve greater inhalation effort (higher PIP) with a high-resistance device compared with the low-resistance device (6.5 kPA for high resistance vs 3.7 kPA for low resistance, $P < 0.01$). Additionally, inhalation time was also significantly greater for the high-resistance DPI (high-resistance: 3.3 s vs low-resistance: 1.7 s; see Fig. 4). This study concluded that using dry powder inhalers with high device resistance may enhance the probability of achieving effective dose delivery [51].

Results from the BREEZE study of patients with PAH showed that this patient population is compatible with Tyvaso DPI [21]. Additionally, studies in patients with ILD or idiopathic pulmonary fibrosis have demonstrated their ability to reach a maximum inspiratory pressure of around 9 kPa [63,64]. These findings demonstrate minimal to no decline in the force-generating capacity of the inspiratory muscles within this patient population. Taken together, the BREEZE study's results, along with other studies in patients with advanced lung disease, demonstrate the compatibility of Tyvaso DPI with patients' inhalation capabilities.

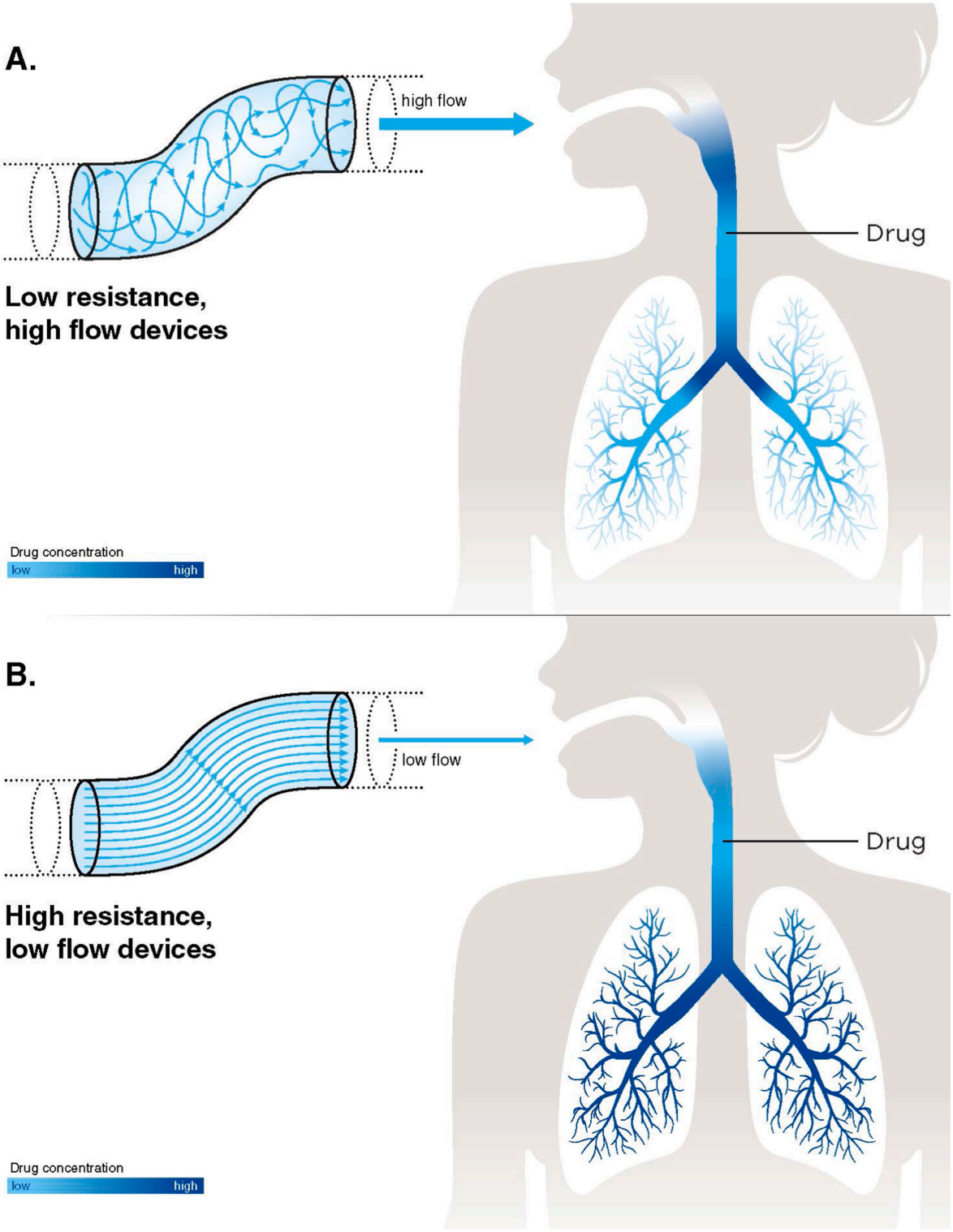

Fig. 3. Airflow and drug deposition from (A) low-resistance, high-flow devices and (B) high-resistance, low-flow devices.

4. Clinical studies with Tyvaso DPI

4.1. Efficacy

BREEZE, an open-label safety and tolerability study of Tyvaso DPI, enrolled 51 patients with PAH (mean pulmonary arterial pressure >25 mmHg, pulmonary vascular resistance >3 Wood units) on a stable regimen of nebulized Tyvaso to transition to a corresponding dose of Tyvaso DPI for 3 weeks, followed by an open-label extension phase (OEP) to assess the long-term safety and tolerability of Tyvaso DPI [21]. Patients were initially assigned a Tyvaso DPI dose (32, 48, or 64 μg) four times per day that corresponded to their current inhalation solution (see Table 2). In the OEP, doses could be titrated upwards.

Six patients reached doses ≥112 μg (corresponding to 23 breaths of nebulized Tyvaso) after a mean treatment time of 51 weeks, and 1 patient reached 176 μg (corresponding to 33 breaths of nebulized Tyvaso).

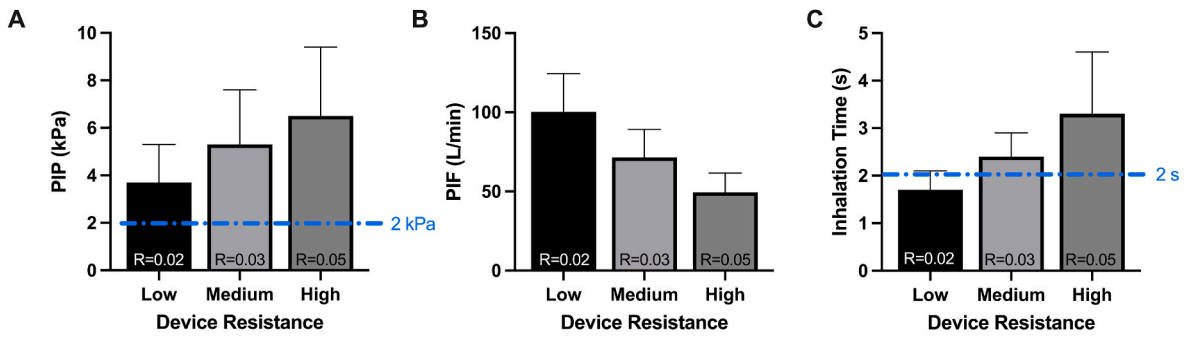

Fig. 4. Impact of device resistance on inspiratory flow profiles of patients with PAH who were instructed to inhale with maximal effort until their lungs were full. A) peak inspiratory pressure (PIP) vs device resistance; B) peak inspiratory flow rate (PIF) vs device resistance; C) inhalation time vs device resistance. Figure adapted from Sahay S, Holy R, Lyons S, Parsley E, Maurer M, Weers J. Impact of human behavior on inspiratory flow profiles in patients with pulmonary arterial hypertension using AOS dry powder inhaler device. *Pulm Circ*. Jan–Mar 2021; 11(1):2045894020985345.

Secondary outcomes included pharmacokinetic evaluations, 6-min walking distance (6MWD), and patient-reported device satisfaction and preference. In total, 49 of 51 (96 %) patients elected to participate in an optional, extension phase. After 3 weeks of treatment, 6MWD improved by 11.5 m ($P = 0.02$), and interim results suggest these improvements were sustained through the extension phase. The improvements in 6MWD may reflect improved patient compliance, but further studies would be needed to confirm this finding. Overall, systemic exposure between the DPI and nebulizer devices was similar in this study (Fig. 5). Notably, these results were obtained with fewer inhalations than required for nebulized treprostinil solution.

4.2. Patient satisfaction and quality of life

In the BREEZE clinical study, patient-reported satisfaction after 3 weeks of use also significantly improved with Tyvaso DPI, with 98 % ($P < 0.0001$) of patients stating they were satisfied with Tyvaso DPI compared with 31 % who preferred nebulizer treatment [21]. Additionally, Pulmonary Arterial Hypertension-Symptoms and Impact questionnaire (PAH-SYMPACT) scores showed improvement in all 4 domains, with significant improvements observed for physical and cognitive/emotional impacts after week 3 ($P = 0.0438$ and $P = 0.0048$, respectively). Patients reported that Tyvaso DPI is easy to travel with, hold, set up, use, load, keep clean, and that the cartridge was easy to remove from the device. The survey also found that patients preferred the handheld size of Tyvaso DPI to the treprostinil nebulizer.

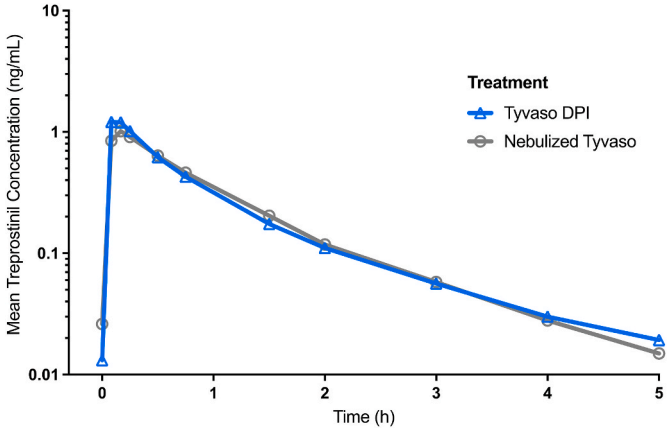

Fig. 5. Comparison of systemic exposure to treprostinil using the treprostinil nebulizer and the Tyvaso DPI.

4.3. Safety and tolerability

Tyvaso DPI was found to be safe and tolerable in patients with PAH who transitioned from nebulized treprostinil. Thirty five percent of patients with PAH in the BREEZE study (32 μg–176 μg) experienced coughing and 16 % experienced headaches with Tyvaso DPI (Table 3) [11,21]. No serious AEs were considered to be related to Tyvaso DPI [21]. Furthermore, the rate of AEs, measured as the number of AEs divided by the total patient years, also declined over time in the OEP of BREEZE (3-week study: 23.6; OEP: 4.3) [21], suggesting that tolerance may improve over time with Tyvaso DPI (Table 3).

5. Clinical considerations for patient selection

In order to ensure optimal treatment outcomes, it is imperative to carefully match the appropriate delivery system with the patient's ability to use it correctly and their level of adherence. DPIs offer a simpler solution compared to other available inhaled drug options, thereby enhancing patient convenience and ease of use. Furthermore, the compact size of DPI devices contributes to their high portability, allowing patients to carry the device discreetly.

Inhaled prostacyclin therapy may be considered in patients receiving initial PAH therapy when there is a desire to escalate treatment with a prostacyclin-class agent [65]. Further, inhaled prostacyclin therapy may be considered in patients where non-invasive therapy is desired. Tyvaso DPI may be considered advantageous in patients with PAH and pulmonary comorbidities, or those patients with mixed Group 1 and Group 3 PH [66]. Other patient characteristics that may lend themselves to preference with inhaled prostacyclin therapy may be patients who cannot tolerate or are not deemed appropriate for oral or parenteral prostacyclins. Due to the pharmacokinetics, inhaled therapy is favorable for patients who struggle with therapy adherence where abrupt discontinuation of systemically administered prostacyclins may be dangerous [67]. Patients with PAH who are already taking inhaled

Table 3
Summary of AEs reported in BREEZE clinical study.

Preferred term, N (%)	Tyvaso DPI	
	BREEZE [21] N = 51	BREEZE OEP [21] N = 49
Cough	18 (35 %)	7 (14 %)
Diarrhea	2 (4 %)	5 (10 %)
Dizziness	0	5 (10 %)
Dyspnea	4 (8 %)	7 (14 %)
Headache	8 (16 %)	4 (8 %)
Nausea	3 (6 %)	–
Throat irritation	2 (4 %)	–

AE, adverse event; DPI, dry powder inhaler; OEP, optional extension phase; -, not reported.

treprostinil tolerate the transition to Tyvaso DPI well [68]. Moreover, patients with PAH or PH-ILD who are motivated to transition away from nebulized treprostinil due to the logistical difficulties, such as the size and complexity of the setup, are also good candidates for Tyvaso DPI. This alternative option offers a more compact and user-friendly design, and the inclusion of prefilled cartridges and the no-maintenance design of the device may be suitable for individuals leading active lifestyles [69,70]. Furthermore, patients may be able to achieve higher doses with Tyvaso DPI than with nebulized treprostinil, facilitating greater long-term improvements in exercise capacity [71]. Due to the ability to titrate to high doses, Tyvaso DPI facilitates transition to parenteral prostacyclins [72].

When starting inhaled treprostinil therapy, it is recommended that patients titrate up to a target maintenance dose of 48–64 μg per session with titration every 1–2 weeks to improve tolerability [10]. Doses with Tyvaso DPI are increased in increments of 16 μg (corresponding to 3 breaths of nebulized Tyvaso) per treatment session four times per day until the target dose is reached [10]. For patients who may be particularly sensitive to AEs such as cough and throat irritation, the Tyvaso nebulizer offers titration in smaller dose increments [11]. This enhanced precision during titration may be more advantageous for patients with PH-ILD.

The ease of use and delivery system of DPIs provide future research opportunities for potential novel applications, such as, PRN (as needed) use before exercise, or to alleviate dyspnea in the emergency room setting for an untreated or undertreated patient. However, data regarding these uses are currently unavailable, emphasizing the need for further exploration. Rigorous studies are required to investigate the feasibility and effectiveness of these potential uses and to determine the optimal dosing strategies for such specific clinical scenarios.

6. Summary

DPIs have been in use for decades as a safe, efficient, and simple way to deliver medications to the lungs while minimizing systemic AEs. The technology has been approved for multiple diseases, including asthma, COPD, diabetes, and recently PAH and PH-ILD [21,32,40]. However, DPI devices vary in important parameters that may change suitability for some patient types.

While many have incorrect beliefs about high-resistance devices, research and real-world clinical evidence have shown that patients with pulmonary disease, including PH, can generate the inspiratory force needed to properly use these devices [21,51,54]. Additionally, low-flow, high-resistance devices improve lung deposition by reducing oropharynx impaction rates [55]. Inspiratory pressure generated by a patient's inspiratory effort is important for controlling DPI device efficacy [55].

Clinical studies of Tyvaso DPI have found that it led to improvements in 6MWD and increased patient satisfaction after switching from nebulized treprostinil [21]. Patients enrolled in BREEZE also experienced mild AEs, and tolerability seemingly improves with time [11,21].

Tyvaso DPI may be considered as a first prostacyclin agent or for those that do not tolerate other prostacyclin agents, patients with pulmonary comorbidities, patients with mixed Group 1 and Group 3 PH, or those that prefer an active lifestyle and need a portable, non-invasive treatment. The dry powder formulation of treprostinil offers a new option that has been approved for use in patients with PAH and PH-ILD.

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Author contributions

All authors were responsible for the development, preparation, and editing of this manuscript.

Declaration of competing interest

CM has received payment or honoraria from United Therapeutics and has participated on a data safety monitoring board or advisory board, for United Therapeutics, Merck, and Janssen Pharmaceuticals. RA is a member of an advisory board, has done disease state specific speaking engagements, and participates in clinical trials sponsored by United Therapeutics. SSa has received payments for speaking (promotional/non-promotional), consulting, and research from United Therapeutics, Liquidia Technologies, Gossamer Bio, Bayer, GlaxoSmithKline, and Janssen/Johnson and Johnson. CME has received payment or honoraria from United Therapeutics and has served on Advisory Boards for United Therapeutics. SSh is involved in research projects with United Therapeutics, Liquidia, Pharmousa, and Gossamer but receives no compensation for this work. CS is an employee of MannKind. CD, TW, BND, and MB are employees of United Therapeutics. CB has participated in multi-center interventional trials sponsored by United Therapeutics and is a consultant for INSMED, Gossamer Bio, and Janssen.

Data availability

No data was used for the research described in the article.

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